



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation Research
Office of Blood Research and Review

To: BL STN 125574/0, Natalya Ananyeva, PhD, Committee Chair and Pratibha Rana, RPM

From: Nancy Kirschbaum, PhD, Product Reviewer

Applicant: Bayer HealthCare Pharmaceuticals, Inc.

Product: Antihemophilic Factor (Recombinant), BAY 81-8973, Kovaltry

Subject: Chemistry, Manufacturing and Controls Product Review

Through: Tim Lee, PhD, Acting Chief, OBRR/DHRR/LH
Basil Golding, MD, Director, OBRR/DHRR

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Scope of Review

Review of the following CTD sections is documented in this memo:

Drug Substance:

- 3.2.S.2.4: Control of Critical Steps and Intermediates
- 3.2.S.2.6: Manufacturing Process Development
- 3.2.S.6: Container Closure System – description

Drug Product:

- 3.2.P.2 Pharmaceutical Development
- 3.2.P.3.4 Control of Critical Steps and Intermediates – excluding lyophilization
- 3.2.P.4 Excipients
- 3.2.P.7 Container Closure System – description, sourcing and control

Introduction

Bayer HealthCare, Inc. has submitted an original biologics license application for Antihemophilic Factor (Recombinant), Kovaltry™. The commercial product is a sterile, non-pyrogenic, lyophilized powder for reconstitution contained in a single-dose vial of nominal potency: 250, 500, 1000, 2000, or 3000 international units (IU). The 250 IU, 500 IU and 1000 IU vials are reconstituted with 2.5 mL sterile water for injection; the 2000 IU and 3000 IU vials are reconstituted with 5 mL. Kovaltry™ is a full length recombinant antihemophilic factor (Coagulation Factor VIII) indicated for use in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: (1) control and prevention of bleeding episodes, (2) perioperative management, and (3) routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Kovaltry™ is not indicated for the treatment of von Willebrand Disease. Clinical trials that provided substantial evidence of safety and efficacy were conducted under IND 14035.

Hemophilia A is a rare, hereditary, hematologic disorder caused by deficiency or dysfunction of Coagulation Factor VIII (historically referred to as Antihemophilic Factor), resulting in bleeding secondary to abnormal clot formation. Because the Factor VIII gene is located on the X-chromosome, Hemophilia A has an X-linked, recessive inheritance pattern, affecting 1 in 5,000 male births with rare occurrence in females. There is no available cure for Hemophilia A. To promote clotting, patients are treated to replace the deficient Factor VIII by intravenous administration of a purified Coagulation Factor VIII (Antihemophilic Factor) concentrate. Both plasma derived and recombinant DNA derived Antihemophilic Factor concentrates are commercially available. Bayer is currently licensed to manufacture and distribute Kogenate F/S. The rationale for Kovaltry development was to improve the manufacturing process licensed for Kogenate F/S. The manufacturing process for Kovaltry has incorporated the following key changes:

1. (b) (4)

[REDACTED]

2. (b) (4)



3. (b) (4)



Kovaltry has not been previously approved for commercial distribution.

Regulatory Process

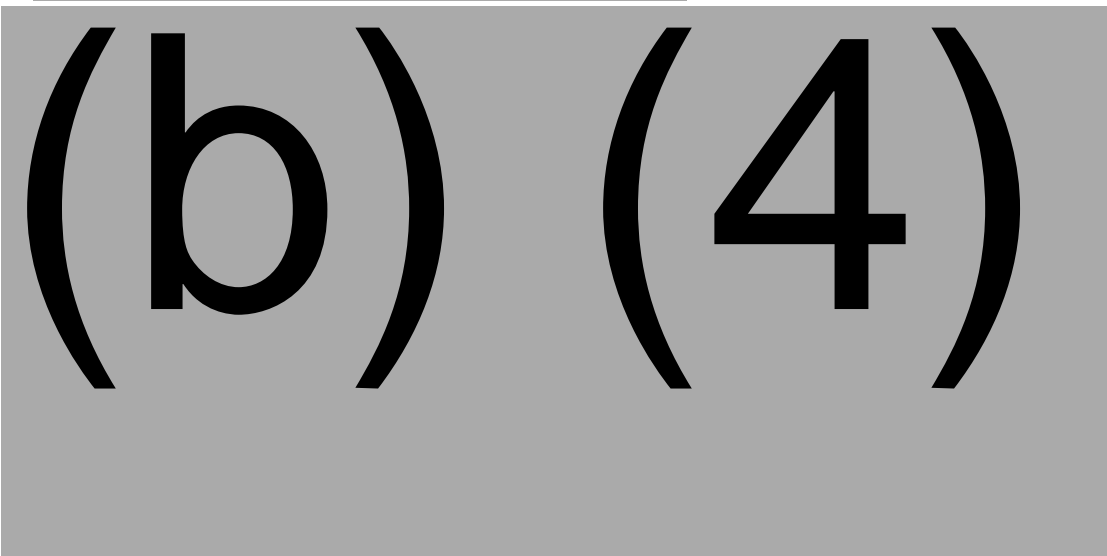



STN BL 125574/0 was reviewed under the PDUFA V program (standard 12 month review); regulatory milestones are listed in Table I-1.

Table I-1: Regulatory Milestones

Milestone	Date
Received	December 16, 2014
First committee meeting	January 8, 2015
Filing memo	February 3, 2015
Filing date	February 9, 2015
Mid-cycle meeting	June 3, 2015
Pre-license inspection	Waived but Team Biologics inspection performed
Late cycle meeting	September 3, 2015
Advisory Committee	Waived
Action Due	December 16, 2015

Drug Substance



(b) (4)



(b) (4)



(b) (4)



(b) (4)



Drug Product

Product Description

Kovaltry™, Antihemophilic Factor (Recombinant) is a sterile, non-pyrogenic, preservative-free, white to slightly yellow powder for reconstitution contained in a single-use vial. The reconstituted product is indicated for intravenous administration. The product is available in 250 IU, 500 IU, 1000 IU, 2000 IU, or 3000 IU nominal potencies. The container closure system consists of a 10 mL, Type I glass vial sealed with a bromobutyl grey stopper and either a reconstitution cap or aluminum crimp seal with plastic flip-off cap plus vial adapter. Both configurations were designed to connect with the sterile water for injection (sWFI), pre-filled diluent syringe.

Overview of the Process

The drug product manufacturing process involves (b) (4) drug substance, (b) (4) (2.2% glycine, 1.0% sucrose, 0.03 M NaCl, 0.0025 M CaCl₂, 0.02 M histidine, 80 µg/mL polysorbate 80, pH (b) (4) to appropriate target potency, sterile filtration, filling into vials, lyophilization and packaging. Sterile filtration is performed on partially formulated (diluted) drug product. Final potency adjustment is achieved by adding formulation buffer through the same sterile filter subject to filter integrity testing. A vial fill volume of 2.5 mL or 5.0 mL is performed depending on final potency.

Pharmaceutical Development – Section 3.2.P.2

Composition – Report P.2.1.50-01

Bayer claimed in report P.2.1.50-01 that BAY 81-8973 has the same formula strengths and formulation as licensed rAHF (Kogenate). *Review issue: Bayer intends to replace the one stage clotting assay with the chromogenic assay for potency assignment. Despite retention of nominal potencies, absolute amount of product per vial will decrease by (b) (4) (see below under, “One Stage vs. Chromogenic Substrate Potency Determination”).*

Product composition in each vial is listed in Table P2-1.

Table P2-1: Product Composition

Component	Function	Quality	250/500/1000 IU 100/200/400 IU/mL	2000/3000 IU 400/600 IU/mL
rFVIII	(b) (4)	Specification		
Sucrose	(b) (4)	(b) (4)	(b) (4) 1%w/v	(b) (4) 1%w/v
Histidine	(b) (4)	(b) (4)	(b) (4) 0.02 M	(b) (4) 0.02 M
Glycine	(b) (4)	(b) (4)	(b) (4) 2.2%	(b) (4) 2.2%
Sodium chloride	(b) (4)	(b) (4)	(b) (4) 0.03 M	(b) (4) 0.03 M
Calcium chloride	(b) (4)	(b) (4)	(b) (4) 0.025 M	(b) (4) 0.025 M
Polysorbate 80	(b) (4)	(b) (4)	(b) (4) 80 µg/mL	(b) (4) 80 µg/mL

Formulation Development – Report 2.2.01-01

Kovaltry was designed to have the same formulations, container closure and fill sizes (2.5 mL and 5 mL) as Kogenate. Stability data supported retaining the Kogenate formulations for Kovaltry.

Physicochemical and Biological Properties – Report P.2.2.04-03

Physicochemical and biological properties were compared among BAY 81-8973 clinical lots, conformance lots and reference standard (RS) (b) (4), and Kogenate lot 27N1190 used in comparative pre-clinical studies. Drug product comparative analysis was an extension of that conducted on drug substance whose results were submitted to section 3.2.S.3.1. Analytical tests focused on higher order structure and biological activity, product quality attributes with impact on drug product performance, as recommended in the ICH Q8 guideline¹. (b) (4),

(b) (4)

Potencies determined by one stage clotting and chromogenic substrate assays were compared. *In vitro* functional assays were employed to enhance product characterization regarding functional activities and intermolecular interactions attributed to Factor VIII biological activity, and to complement physicochemical characterization to provide an *in vitro* link between molecular attributes and important physiological functions. Bayer characterized vWF binding by (b) (4)

. Table P2-2 lists drug product lots included in comparative analyses.

Table P2-2: Lots for Comparative Analysis

Lot number	Vial Potency (IU)	Use
RS 0090 RM2	1000	Initial reference standard
27N1R50	1000	Pre-clinical/Clinical I
27N1TR0	1000	Pre-clinical/Clinical I
27N1WJ0	250	Clinical I
27N1WL0	500	Clinical I
27N2750	2000	Clinical I
27N1190/Kogenate	1000	Licensed product
27N2C80	250	Clinical II
27N2KH0	1000	Clinical II
27N2KJ0	2000	Clinical II
27N2KK0	500	Clinical II
27N2KN0	1000	Clinical II
27N29K0	1000	Clinical II
27N29L0	1000	Stability/Clinical II
(b) (4)	2000	Conformance, Future reference standard
(b) (4)	1000	Conformance
(b) (4)	2000	Conformance
(b) (4)	250	Conformance
(b) (4)	3000	Conformance
(b) (4)	3000	Conformance
(b) (4)	3000	Conformance
(b) (4)	250	Conformance
(b) (4)	500	Conformance

Analytical comparability for all tests was demonstrated among all lots.

One Stage vs. Chromogenic Substrate Potency Determination

The one stage clotting (OS) clotting assay is used to control Kogenate manufacture and label the drug product. Bayer has developed BAY 81-8973 with the intent of labeling drug product using the chromogenic substrate (CS) assay. Comparative analyses between the two assays were conducted throughout pre-market development because discrepant values are commonly reported for recombinant products⁵. The Kogenate release assay on the (b) (4) against the (b) (4) reference standard was initially used to set the “chromogenic adjusted potency” investigated as part of BAY 81-8973 clinical study. Later in pre-market development, OS potency was assigned using a BAY 81-8973 product specific standard calibrated against (b) (4) WHO (b) (4) international standard (IS) or WHO (b) (4) IS, depending on the study. Details regarding the

⁵ Hubbard AR. Potency Labeling of Novel Factor VIII and Factor IX Concentrates: Past Experience and Current Strategy. (2015) Seminars in Thrombosis and Hemostasis

CS were not provided in [report P.2.2.04-03](#). The intended release assay using the (b) (4) was submitted to [section 3.2.P.5.2](#) in [report P.5.2.60-01](#). In total, three comparative analytical studies were conducted to compare OS and CS potency values: (1) “Study to Set the ‘Chromogenic–Adjusted (CS-ADJ)’ Labelled Potency,” (2) “Extended Characterization Study of Each DP Lot,” and (3) “Studies using WHO International Standard Assignments.”

Study to Set the “Chromogenic–Adjusted (CS-ADJ)” Labelled Potency

The following comparative data listed in Table P2-3 were generated for three Kogenate and four BAY 81-8973 lots, covering 250 IU, 500 IU and 1000 IU nominal potency vials. Vials were reconstituted with 2.5 mL diluent.

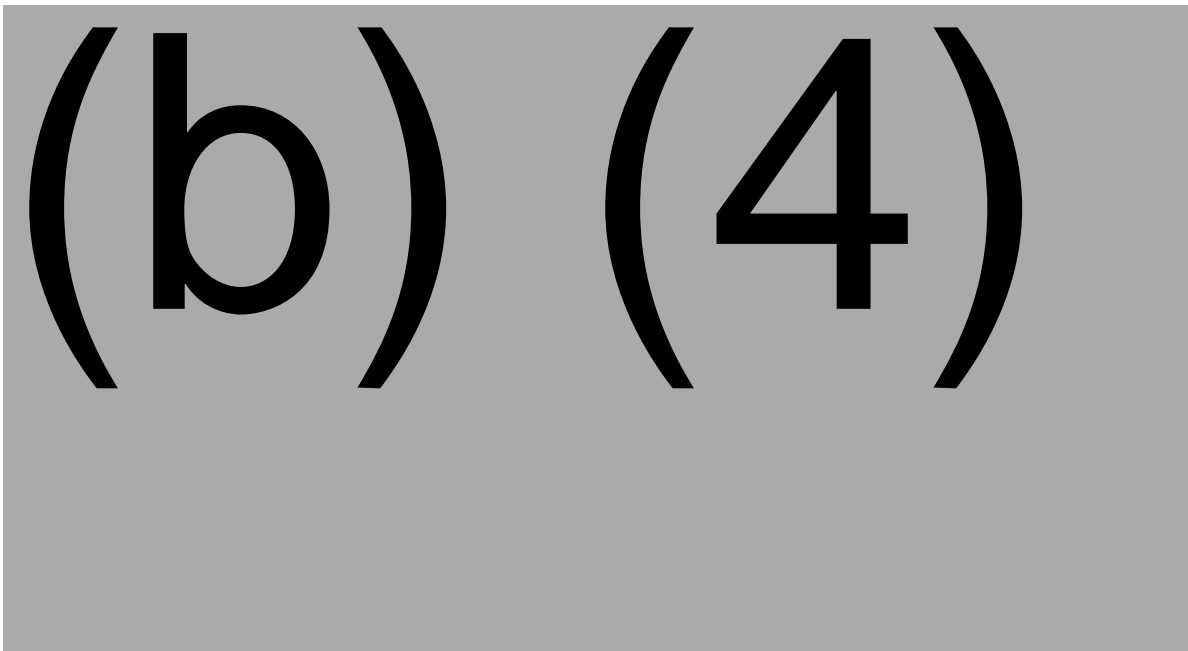
Table P2-3: Chromogenic Substrate vs. One Stage Potency Determination I

Lot number	Product	CS IU/mL	OS IU/mL	CS/OS
(b) (4)	Kogenate	(b) (4)	(b) (4)	(b) (4)
(b) (4)	Kogenate	(b) (4)	(b) (4)	(b) (4)
(b) (4)	Kogenate	(b) (4)	(b) (4)	(b) (4)
(b) (4)	BAY 81-8973	(b) (4)	(b) (4)	(b) (4)
(b) (4)	BAY 81-8973	(b) (4)	(b) (4)	(b) (4)
(b) (4)	BAY 81-8973	(b) (4)	(b) (4)	(b) (4)
(b) (4)	BAY 81-8973	(b) (4)	(b) (4)	(b) (4)
Ratio average				(b) (4)

Extended Characterization Study of Each DP Lot

Throughout pre-market development, each drug product lot was evaluated for potency by both CS and OS assays. [Report P.2.2.04-03](#) indicated use of the release CS assay (i.e., (b) (4) and use of a “recombinant standard” calibrated against either (b) (4) or the WHO IS for the OS assay. Further statistical analyses were conducted for comparative assessment of CS vs. OS values across nominal potency vials. Table P2-4 lists comparative potency values.

Table P2-4: Chromogenic Substrate vs. One Stage Potency Determination II



(b) (4)

Studies Using WHO International Standard Assignments

As reflected in Table P2-4, Bayer employed a number of in-house reference standards assigned against different primary reference standards (b) (4) or WHO IS) for potency determination throughout pre-market development. Although the first five clinical lots had been assigned potencies by OS and CS assays using the same in-house reference standard, CS potencies for subsequent lots were assigned using a different standard than that used for OS potency assignment of the same lot. As an attempt to further characterize CS/OS relative potency using the same reference standard, Bayer calibrated (b) (4) (b) (4) (which had been used to assign CS potencies to conformance lots) against the WHO (b) (4) IS using the OS assay for OS retesting of conformance lots. Table P2-5 lists comparative values.

Table P2-5: Chromogenic Substrate vs. One Stage Potency Determination III

(b) (4)

Review discussion on potency assay for Kovaltry labeling: Bayer presented comparative data to support its stated conclusion, "While the initial data indicated the ratio of the CS to OS was (b) (4) further lots and testing over the years, using a variety of recombinant standards and assignments, indicates the assay results are closer together with the average ratio being approximately (b) (4) The results presented appeared to indicate a trend toward decreased CS/OS discrepancy over time; however, revealed a significant degree of variability, with no assignable pattern respective of assay or primary reference standard (b) (4) WHO (b) (4) IS, WHO (b) (4) IS) used for calibration of in-house potency standards. Therefore, this reviewer concluded from the submitted data that depending on reference standard calibration and assay, (b) (4) less product will be filled into Kovaltry vials containing the same nominal potencies currently labeled for Kogenate.

Manufacturing Process Development

Manufacturing process development focused on evaluating the suitability for Kovaltry manufacture of the currently licensed process for Kogenate. One manufacturing change was implemented – addition of (b) (4) in the drug product manufacturing process. As one piece of evidence supporting suitability, Bayer submitted in [section 3.2.P.5.4 Batch Analysis – Development \(report P.5.4.02-02\)](#), release results for 17 drug product lots manufactured at commercial scale and used during clinical development. All lots met specification in place at the time of each lot's release. Analytical results appeared similar to release results submitted for conformance lots ([section 3.2.P.5.4 Batch Analyses, report P.5.4.01-02](#)). In addition, stability monitoring of clinical lots yielded conforming results ([section 3.2.P.8.3 Stability Data – Clinical Trial Batches, report P.8.3.30-02](#)). Bayer also performed scaled down, process evaluation studies to assess suitability. (b) (4), scaled down lots – (b) (4) (250 IU/vial) and (b) (4) (2000 IU/vial) – were manufactured according to the licensed manufacturing procedure employing validated critical process parameters using smaller processing equipment. Release results submitted in [report P.2.3.50-01](#) met the clinical drug product release specification in place at that time.

(b) (4)

(b) (4)

Excipients – Section 3.2.P.4

Excipients used in formulating the final drug product include glycine, L-histidine, sodium chloride, calcium chloride, polysorbate 80 and sucrose. Documentation of the in-house quality standard for each excipient submitted in [section 3.2.P.4](#) indicated a requirement to conform with each respective (b) (4).

Container Closure – Section 3.2.P.7

Description

The drug product primary container closure system comprises a 10 mL, (b) (4), Type I glass vial closed with a bromobutyl grey stopper. There are two options for the over seal: (1) (b) (4) aluminum with plastic flip-off top or (2) reconstitution cap.

Control of Components

Table P7-1 summarizes quality and control information for each container closure component.

Table P7-1: Control of Container Closure Components

Component	Materials of Construction	Material Specification	Supplier	DMF
Vial, 10 mL, 20 mm neck	Type I, clear, tubing glass with (b) (4)	(b) (4)	(b) (4)	(b) (4)
Stopper, 20 mm	Bromobutyl grey (b) (4) (b) (4)	(b) (4)	(b) (4)	(b) (4)
Seal	(b) (4) aluminum with plastic flip-off top	---	(b) (4)	---
BIO-SET (b) (4) reconstitution cap containing cap, base and needle/luer assembly	(b) (4)	(b) (4)	Baxter	(b) (4)

Information Requests and Amendments

Requests for additional information for all review disciplines were conveyed to Bayer throughout the review cycle. Table IR-1 provides a history of information requests (IR) associated with the review scope described in this memo.

Table IR1: Product Information Requests and Amendment Responses

IR Date	Subject	Amendment Response
June 29, 2015	1. Process control strategy 2. Establish (b) (4) specification 3. Submit master batch records	<ul style="list-style-type: none"> Amendment /0.18 received on July 24, 2015 contained copies of the master batch records. Amendment /0.19 received on July 31, 2015 contained process control strategy for each unit operation and (b) (4) specification
July 10, 2015	1. (b) (4) storage stability 2. Control strategy term definition 3. Inadequacy of small-scale studies re: (b) (4) 4. Submission of a comparability report	<ul style="list-style-type: none"> Amendment /0.19 received on July 31, 2015 contained control strategy term definitions Amendment /0.22 received on August 10, 2015 contained information addressing (b) (4) storage stability, control strategy term definition, information to address inadequacies in small scale studies, comparability report
July 23, 2015	Suppliers and letters of authorization for container closure components	Amendment /0.28 received on September 1, 2015 contained the requested information.

Conclusion

All outstanding issues related to the review scope of this memo have been resolved.